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Neurophysiological Alterations due to Diesel Exhaust Exposure during the Neonatal Life of the Rat

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16. ABSTRACT
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NEUROPHYSIOLOGICAL ALTERATIONS DUE TO DIESEL EXHAUST EXPOSURE DURING THE NEONATAL LIFE OF THE RAT

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This study was designed to assess the effects of diesel exhaust on the development of the nervous system in rats as measured by somatosensory and visual evoked potentials (SEPs and VEPs, respectively). SEPs, elicited by 1 mamp, 0.5 msec pulses delivered to the tibial nerve at the tibale, were recorded from the skull overlying the somatosensory projection area on days 28, 35, 42, and 49 postconception (pc). Analysis of the data for day 35 pc double pulse SEPs revealed significantly longer latencies for all peaks of the SEP in pups exposed to diesel exhaust. There were also differences indicating that the electrophysiological recoverability of the nervous system had been compromised in the diesel exhaust exposed group. On day 35 pc, the latencies of all VEP peaks occurring before 300 msec were greater in the exposed group. The differences, however, reached statistical significance only for the P2 peak of the response to the first of the paired stimuli. These data support the hypothesis that diesel exhaust influences the development of the nervous system.

Introduction

Data from a previous experiment revealed that exposure to diesel exhaust during the neonatal life of rats delayed the day of eye opening and reduced the amount of pivoting behavior displayed on days six and seven post-parturition (Laurie *et al.*, 1978). Two further experiments, reported in a companion paper (Laurie *et al.*, 1979), indicated that the behavioral alterations resulting from neonatal exposure to diesel exhaust were not transient, but persisted throughout the lifetime of the rat. The first experiment clearly associated neonatal diesel exhaust exposure with decreased adult spontaneous locomotor activity. The second experiment indicated that the exposure of neonates to diesel exhaust produced differences in the acquisition of a relatively simple bar pressing task when the animals were 15 months of age.

The present study was designed to assess the effects of diesel exhaust on the development of the nervous system as measured by somatosensory and visual evoked potentials (SEPs and VEPs, respectively), collected from rat pups on days 28, 35, 42, and 49 postconception (pc).

Methods

Exposure

A general description of the exposure situation and the average levels of diesel exhaust components are reported elsewhere (Laurie *et al.*, 1981). The exposure system is described in detail by Hinners *et al.* (1979). Briefly, the diesel exhaust animals were exposed for eight hours per day, seven days per week to diesel exhaust generated by a Nissan CN 6–33. The particulate matter concentration was maintained at approximately 6 mg/m^3 by dilution with filtered air.

Animal care

Sixty pregnant Sprague Dawley rats were ordered from the Michigan Charles Rivers animal supply laboratory. Fifteen dams were bred on each of four consecutive days. This design provided four experimental days to examine each tested day of pup development.

On day one after parturition, each litter was culled to eight pups, leaving four, five, or preferably six males per

litter. Litters containing less than four males, or less than eight total pups, were excluded from the study. In addition to matching the litters for number and sex of pups, the following parameters were matched: day of conception, length of gestation, beginning time of parturition, number and weight of the pups per litter, and ratio of males to females. Of the initial 60 pregnant rats, 41 litters were matched and randomly placed into either the control or the exposed group.

Electrophysiology

General procedure. The development of the SEP and the VEP was monitored from postconception day 28 or 35, respectively, through day 49. Rat pups are more maturationally similar compared to the time of conception than compared to the time of parturition. Therefore, the evoked potentials were evaluated in reference to conception as a means of reducing data variability.

When the pups reached the designated age of testing, they were anesthestized with pentobarbital at doses of 30 mg/kg (day 28 pc), 40 mg/kg (day 35 pc) or 50 mg/kg (days 42 and 49 pc). They were then placed in a stereotaxic apparatus modified to accommodate small animals, the skull was exposed, and silver ball electrodes were placed on the skull. Electrical brain activity was amplified by a Textronix 26A2 Differential Amplifier (0.1 to 10 kHz, 3 dB Band width) and then sent to four inputs: (1) oscilloscope, (2) Nicolet 1170 signal averager, (3) Nicolet spectrum analyzer, and (4) multitrack tape recorder for data storage.

Somatosensory evoked potential. The SEP was elicited by 1 mamp pulses of 0.5 msec duration, delivered to the tibial nerve of the left hind limb at the tibale. Evoked potentials were recorded from an active electrode located on the skull above the somatosensory projection area, 2 mm lateral to bregma. The reference electrode was 6 mm anterior to the active electrode. The stimuli for day 28 pc were presented to the pups in three sets of 128 single pulses. The data included the averaged peak latencies and amplitudes from the first and third sets of stimuli. On days 35, 42, and 49 pc, 128 double pulse stimuli, with interstimulus intervals of 300, 200, and 150 msec, respectively, were presented and averaged at a rate of 0.5 Hz. The data consisted of latencies and amplitudes of the various peaks following each stimulus of the double pulse paradigm. The frequency spectrum of all electroencephalograms was monitored in order to investigate the level of anesthesia.

Visual evoked potentials. The visual system matures more slowly than the somatosensory system. Therefore, VEPs were not obtained on day 28 pc, and longer ISIs were employed for the double pulse paradigm on days 35 and 42 pc (800 and 300 msec, respectively). By day 49 pc, the visual system could respond to the same ISI (150 msec) being used for the SEPs. Dark adaptation of the pups was accomplished during the time the SEPs were being elicited. The VEPs were recorded from above the visual projection area of the right hemisphere (2 mm lateral, and 6 mm posterior to bregma). Placement of the reference electrode was 6 mm anterior to the active electrode.

Results

Somatosensory evoked potentials

Figures 1, 2, and 3 are examples of SEPs elicited on days 28, 35, and 42 pc, respectively. A day 49 pc response has not been included because of its similarity to the day 42 pc SEP. The most prominent feature of the evoked potential on day 28 pc was a negative peak labeled N2. On all days except day 28 pc, the evoked potential waveforms consisted of a series of positive and negative going peaks. The peaks were labeled, beginning at the stimulus artifact of the first pulse as P11, N11,

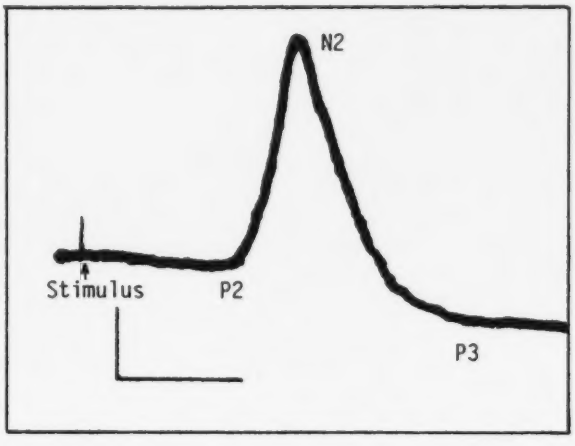

Fig. 1. Typical SEP from a day 28 postconception, male rat. Calibration is 10 μV and 50 msec.

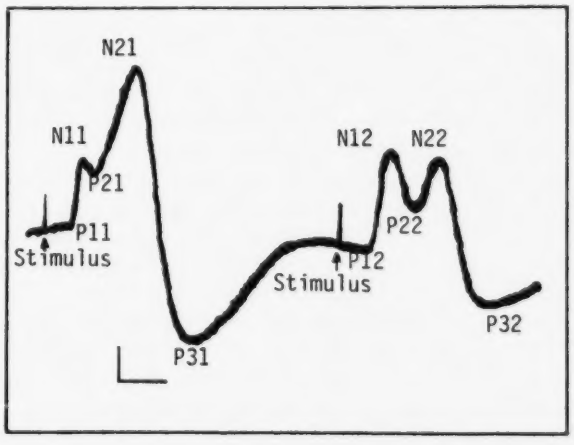

Fig. 2. Typical SEP from a day 35 postconception, male rat. Calibration is 20 μV and 50 msec.

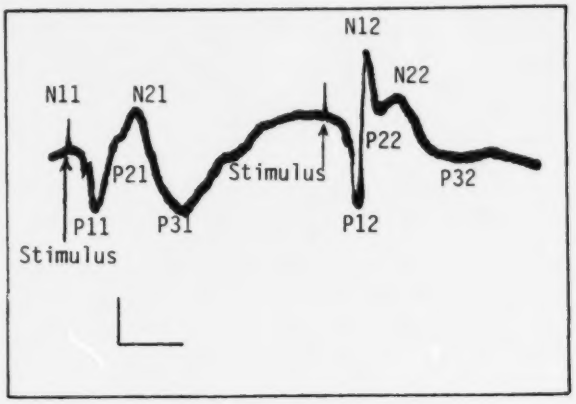

Fig. 3. Typical SEP from a day 42 postconception, male rat. Calibration is 20 μV and 50 msec.

P21, etc., and beginning at the second stimulus artifact as P12, N12, etc. Tables 1 and 2 are summaries of the peak latency and amplitude data, respectively, obtained from the four days tested. On the days when the double pulse paradigm was employed, the peaks of the second evoked potential were usually slower and of different amplitude than the corresponding peaks of the first response.

The most significant differences between the control and exposed groups manifested themselves on day 35 pc. Figure 4 consists of group composite waveforms produced from all SEPs taken on day 35 pc; i.e., 1792 double pulse SEPs per group (128 averages per animal × 14 animals per group). The top waveform is the response to the first stimulus of the double pulse paradigm; the bottom waveform is the response to the second stimulus. The boxes around each peak indicate the standard error of the mean for both latency and amplitude. A comparison between the control composite and the diesel exhaust exposed composite reveals two major differences. First, all latencies to the various peaks are significantly longer for the diesel exhaust exposed group. Second, the difference between the N2 latency in the response to the first stimulus and N2 latency in the response to the second stimulus is significantly longer in the diesel exposed group than in controls. This relationship also exists for P3 latencies. These results are an indication of slower electrophysiological recovery in the central nervous system of neonatal rats exposed to diesel exhaust as compared to control animals. Day 35 pc is the only experimental day in which consistent statistically significant differences are detected.

Visual evoked potentials

The VEP waveforms are visually similar to the SEP waveforms already presented. Tables 3 and 4 are summaries of the VEP latency and amplitude data,

Table 1. Latencies to various peaks of somatosensory evoked potentials taken from male rat pups on days 28, 35, 42, and 49 postconception.

Day PC	Exposure Condition	Response	P1	N1	P2	N2	P3
	Control	1st 128			62.7 ± 1.3	86.1 ± 1.0	140.2 ± 3.9
	Exhaust	Single Pulses			61.6 ± 0.8	86.0 ± 1.5	138.3 ± 3.7
28							
	Control	3rd 128			66.0 ± 1.5	88.6 ± 7.0	144.9 ± 4.9
	Exhaust	Single Pulses			66.0 ± 2.1	87.3 ± 1.2	141.5 ± 5.2
	Control	1st of	22.9 ± 0.7[A]	34.3 ± 1.0[A]	45.1 ± 1.6[B]	83.4 ± 2.1[A]	131.8 ± 3.5[A]
	Exhaust	Paired Pulses	25.0 ± 0.6	38.0 ± 0.9	51.8 ± 1.0	88.9 ± 1.6	143.1 ± 3.2
35							
	Control	2nd of	24.5 ± 0.8[A]	42.0 ± 1.4[A]	63.3 ± 2.9[B]	88.3 ± 4.1[B]	130.6 ± 6.1[C]
	Exhaust	Paired Pulses	28.3 ± 0.9	47.1 ± 1.2	74.4 ± 2.1	104.8 ± 3.3	155.4 ± 3.
	Control	1st of	22.2 ± 0.7	41.4 ± 2.8		56.1 ± 3.2	92.9 ± 2.7
	Exhaust	Paired Pulses	20.9 ± 0.4	43.0 ± 2.4		57.8 ± 5.9	93.4 ± 2.5
42							
	Control	2nd of	23.0 ± 0.8	33.1 ± 1.1	41.4 ± 1.1	53.7 ± 1.1	93.4 ± 3.5
	Exhaust	Paired Pulses	22.2 ± 0.5	32.3 ± 1.0	38.9 ± 1.0	51.2 ± 1.0	87.6 ± 2.7
	Control	1st of	21.8 ± 0.4	30.3 ± 0.7[A]	36.8 ± 1.1	54.0 ± 1.1	93.9 ± 4.3
	Exhaust	Paired Pulses	22.2 ± 0.6	34.1 ± 1.4	39.3 ± 1.1	55.5 ± 1.6	94.6 ± 4.3
49							
	Control	2nd of	25.5 ± 0.8	34.5 ± 0.7	42.6 ± 1.7	57.1 ± 1.7	107.0 ± 5.2
	Exhaust	Paired Pulses	26.8 ± 1.4	36.1 ± 1.0	42.0 ± 1.7	61.0 ± 2.5	110.0 ± 5.4

A = $P < 0.050$.
B = $P < 0.010$.
C = $P < 0.005$.

Table 2. Amplitudes of various peaks of somatosensory evoked potentials taken from male rat pups on days 28, 35, 42, and 49 postconception.

Day Pc	Exposure Condition	Response	P1	N1	P2	N2	P3
	Control	1st 128			−0.6. ± 0.8	−23.4 ± 2.8	5.8 ± 0.9
	Diesel	Single Pulses			0.8 ± 0.4	−20.4 ± 2.9	5.6 ± 1.2
28							
	Control	3rd 128			0.3 ± 0.4	−26.6 ± 4.9	5.5 ± 1.4
	Diesel	Single Pulses			0.7 ± 9.2	−29.7 ± 5.6	7.2 ± 1.5
	Control	1st of	0.5 ± 0.7	−25.9 ± 2.0	−18.4 ± 2.0	−64.8 ± 6.9	45.8 ± 2.8
	Diesel	Paired Pulses	0.2 ± 0.6	−28.6 ± 1.8	−17.5 ± 1.9	−60.0 ± 5.1	46.8 ± 4.0
35							
	Control	2nd of	1.5 ± 1.1	−32.2 ± 4.5	−10.8 ± 3.4[A]	−33.5 ± 5.0	28.2 ± 2.9
	Diesel	Paired Pulses	2.4 ± 0.7	−28.4 ± 2.0	−3.0 ± 2.7	−25.8 ± 3.8	29.3 ± 3.9
	Control	1st of	20.9 ± 3.2	−19.9 ± 5.4		−14.1 ± 4.4	28.4 ± 4.8
	Diesel	Paired Pulses	26.2 ± 3.4	−31.6 ± 16.3		−17.7 ± 8.9	37.1 ± 5.9
42							
	Control	2nd of	26.4 ± 7.0	−20.0 ± 6.3	−5.7 ± 2.3	−14.3 ± 3.0	13.7 ± 2.1
	Diesel	Paired Pulses	38.3 ± 5.5	−19.5 ± 5.5	−7.4 ± 3.2	−21.0 ± 4.0	23.9 ± 5.1
	Control	1st of	72.3 ± 12.1	−7.0 ± 6.0	−7.0 ± 6.0	−46.6 ± 8.0	21.8 ± 4.1
	Diesel	Paired Pulses	80.0 ± 10.0	−6.9 ± 8.9	−2.2 ± 6.2	−43.9 ± 6.0	19.0 ± 5.1
49							
	Control	2nd of	78.6 ± 8.0	−23.3 ± 8.8	−5.7 ± 5.7	−28.9 ± 5.4	26.9 ± 7.4
	Diesel	Paired Pulses	82.4 ± 12.3	−16.3 ± 12.9	−1.4 ± 5.8	−27.7 ± 6.6	16.8 ± 3.7

A = $P < 0.05$.

respectively, obtained on days 35, 42, and 49 pc. On day 35 pc, the latencies of all VEP peaks occurring before 300 msec were greater than controls, but the differences reached statistical significance for only the P2 peak of the response to the first stimulus.

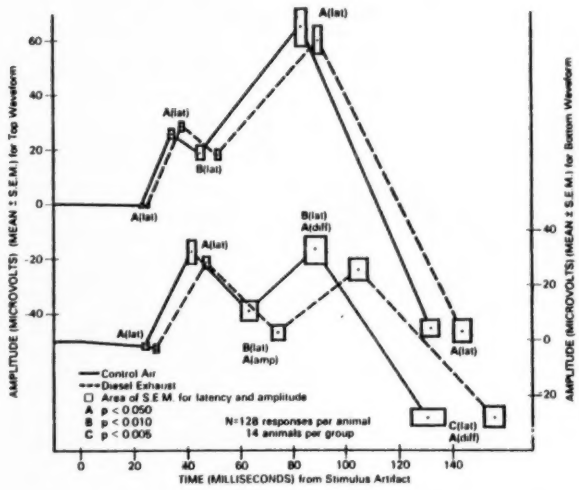

Fig. 4. Group composite waveforms of day 35 postconception (pc) double plus somatosensory evoked potentials from animals exposed to either control air or diesel exhaust from day 22 or 23 pc. Interstimulus interval between top and bottom waveforms is 300 msec. Double pulse delivered at a rate of 0.5 Hz.

Discussion

Significant differences between control and diesel exhaust exposed neonates were detected for developing SEPs and VEPs. The electrophysiological differences can be attributed to differences between the nervous systems of the two groups. The exhaust exposure may affect both the central and peripheral nervous systems (CNS and PNS). For example, the slower latencies to the various peaks may be an indication of decreased myelination in both the CNS and PNS. CNS effects can be hypothesized by regarding the recoverability differences. The ability to follow rapid stimulation is limited by synaptic phenomenon. Because all of the synapses involved with the SEP are located in the CNS, the recovery disparity between the control and exposed groups can be attributed to a lesion(s) in the CNS.

SEP alterations were found in the diesel exhaust exposed group on day 35 pc and not on other days of testing. This may be related to the extremely rapid rate of neural growth and development which occurs in the rat around day 35 pc (approximately day 14 postparturition) (Dobbing, 1970). Among the processes occurring prior to and during this period are cell migration, axon myelination, cell differentiation, synaptogenesis, and elimination and stabilization of neuronal connections (Jacobson, 1978). In particular, the rate of increase in rat brain weight peaks around day 10 postparturition, and the in brain cholesterol around day 16 postparturition (Dobbing, 1970). The rapid rate of neutral growth is reflected in rapidly changing evoked

Table 3. Latencies to various peaks of visual evoked potentials taken from male rat pups on days 35, 42, and 49 postconception.

Day	Exposure Condition	Response	P1	N1	P2	N2	P3	N3
35	Control	1st of	74.2 ± 3.4	102.4 ± 4.3	142.5 ± 4.5[C]	166.7 ± 4.7	231.0 ± 5.8	355.5 ± 14.9
	Diesel	Paired Pulses	79.9 ± 3.5	110.7 ± 5.4	161.5 ± 4.0	179.7 ± 5.5	247.5 ± 10.1	351.4 ± 16.8
	Control	2nd of	77.2 ± 3.3	110.8 ± 4.7	151.3 ± 16.1	169.5 ± 17.2	225.6 ± 6.6	337.6 ± 13.2
	Diesel	Paired Pulses	79.1 ± 3.1	113.8 ± 4.8	167.7 ± 12.4	198.3 ± 3.9	217.7 ± 15.1	334.4 ± 20.9
42	Control	1st of	15.4 ± 3.2	24.8 ± 1.6	38.3 ± 1.2	51.4 ± 1.9	138.0 ± 4.7	193.8 ± 5.1
	Diesel	Paired Pulses	15.7 ± 2.1	24.9 ± 1.6	36.5 ± 0.6	48.7 ± 0.8	139.2 ± 4.7	195.5 ± 4.1
	Control	2nd of	22.1 ± 2.3	32.2 ± 2.5	40.4 ± 1.6	59.3 ± 2.2	118.8 ± 6.0	183.0 ± 7.2
	Diesel	Paired Pulses	15.0 ± 4.4	29.9 ± 1.5	41.7 ± 1.0	59.7 ± 2.1	121.4 ± 5.8	201.3 ± 6.1
49	Control	1st of	13.2 ± 2.2	24.0 ± 0.6	33.6 ± 0.5	47.5 ± 0.7	92.7 ± 3.8	111.6 ± 6.7
	Diesel	Paired Pulses	14.1 ± 3.1	24.5 ± 1.0	34.3 ± 0.7	50.4 ± 2.8	93.3 ± 4.6	104.2 ± 6.8
	Control	2nd of	25.1 ± 3.9	33.1 ± 0.6[A]	43.4 ± 0.9	53.8 ± 0.8	94.7 ± 3.0	104.9 ± 7.7
	Diesel	Paired Pulses	31.1 ± 2.0	36.7 ± 1.5	44.5 ± 1.3	59.4 ± 3.5	97.9 ± 2.8	126.9 ± 8.5

A = $P < 0.05$.
C = $P < 0.005$.

Table 4. Amplitudes of various peaks of visual evoked potentials taken from male rat pups on days 35, 42, and 49 postconception.

Day	Exposure Condition	Response	P1	N1	P2	N2	P3	N3
35	Control	1st of	3.3 ± 1.0	−26.8 ± 3.6	−5.4 ± 2.5	−11.8 ± 3.1	15.4 ± 1.6	3.7 ± 1.0[A]
	Diesel	Paired Pulses	7.7 ± 2.8	−41.6 ± 14.9	−1.1 ± 2.1	−4.4 ± 2.4	19.1 ± 3.7	−0.1 ± 1.3
	Control	2nd of	5.4 ± 1.8	−24.8 ± 5.2	−0.7 ± 7.5	−3.86 ± 6.1	16.0 ± 2.4	−3.6 ± 1.5
	Diesel	Paired Pulses	4.6 ± 2.2	−32.5 ± 8.1	5.5 ± 4.7	1.4 ± 7.6	14.3 ± 4.5	−2.6 ± 1.5
42	Control	1st of	1.7 ± 0.5	−0.2 ± 0.7	23.4 ± 4.1	−28.9 ± 4.0[A]	19.4 ± 2.7	−12.8 ± 2.5
	Diesel	Paired Pulses	2.3 ± 0.8	−0.6 ± 0.9	34.6 ± 6.5	−60.3 ± 12.1	21.9 ± 6.1	−17.7 ± 3.1
	Control	2nd of	2.8 ± 2.7	−0.1 ± 2.5	16.6 ± 3.2	−28.9 ± 6.4	8.3 ± 3.2	−14.4 ± 5.2
	Diesel	Paired Pulses	5.8 ± 2.9	−0.2 ± 2.5	18.4 ± 3.4	−27.7 ± 5.8	11.9 ± 4.5	−17.0 ± 3.5
49	Control	1st of	2.0 ± 1.1	−1.5 ± 1.2	106.0 ± 2.6	−79.1 ± 19.2	26.5 ± 7.9	−3.7 ± 1.0[A]
	Diesel	Paired Pulses	1.6 ± 1.0	−10.4 ± 8.7	58.1 ± 26.2	−91.0 ± 20.8	27.2 ± 7.4	0.1 ± 1.3
	Control	2nd of	0.2 ± 8.2	−13.8 ± 10.4	81.8 ± 26.7	−69.9 ± 26.6	58.9 ± 14.2	−3.6 ± 1.5
	Diesel	Paired Pulses	9.4 ± 3.7	−6.0 ± 10.8	29.4 ± 13.3	−59.0 ± 13.1	38.3 ± 9.4	−2.6 ± 1.5

A = $P < 0.05$.

potential waveforms recorded around day 35 pc. A toxic effect which alters or retards development would produce a larger absolute difference between control and exposed waveforms around day 35 pc than on the other days tested. Specifying the particular process(es) affected by diesel exhaust without further study of development under exposure conditions is difficult because each developmental stage is highly dependent on the successful completion of previous events.

It should also be realized that disruption to any of the growth processes may result in permanent sequale. Male siblings of the animals used in this experiment were monitored, as adults, for spontaneous locomotor activity (SLA). The results of the SLA experiment indicated that the adults, exposed to diesel exhaust as neonates, were significantly less active than control animals (Laurie *et al.*, 1981). Other behavioral experiments involving diesel exhaust exposed animals have been reported in a companion paper (Laurie *et al.*, 1981).

The electrophysiological data reported here suggests that the long-term behavioral alterations produced by neonatal diesel exhaust exposure are related to the failure to develop a normally functioning nervous system. The long-term nature of the behavioral aberrations demonstrates that (1) developmental alterations are not countered during subsequent nonexposure periods; (2) neonatal rats are more sensitive than adults to diesel

exhaust exposure; and (3) the effects in neonates are qualitatively different from the transient depression of activity produced in exposed adult rats (Laurie *et al.*, 1978; Laurie *et al.*, 1981).

Most investigations of diesel exhaust toxicity have employed adult animal exposure. The investigations of possible developmental effects have used classical teratological endpoints and have not investigated the functional competence of the pups (Werchowski *et al.*, 1980a; 1980b). With the projected increase in the number of diesel-powered light duty passenger vehicles, a growing number of developing humans will be exposed to diluted diesel exhaust. In order to help assure the protection of these sensitive individuals, the effects of diesel exhaust on developmental processes should be investigated further.

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